

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
24 August 2000 (24.08.2000)

PCT

(10) International Publication Number
WO 00/48583 A3

- (51) International Patent Classification⁷: A61P 25/06. (81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, L, I, K, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW.
- (21) International Application Number: PCT/US00/03897
- (22) International Filing Date: 16 February 2000 (16.02.2000)
- (25) Filing Language: English (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (26) Publication Language: English
- (30) Priority Data:
09/253,278 19 February 1999 (19.02.1999) US
- (71) Applicant: POZEN INC. [US/US]; Suite 240, 6330 Quadrangle Drive, Chapel Hill, NC 27514 (US). Published:
— With international search report.
- (72) Inventor: PLACHETKA, John, R.; 321 Silver Creek Trail, Chapel Hill, NC 27514 (US). (88) Date of publication of the international search report:
7 December 2000
- (74) Agent: SANZO, Michael, A.; Vinson & Elkins L.L.P., 2300 First City Tower, 1001 Fannin, Houston, TX 77002-6760 (US).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A3

WO 00/48583 (54) Title: FORMULATION OF 5-HT AGONISTS WITH NSAIDS, ESPECIALLY COX-2 INHIBITORS, FOR TREATING MIGRAINE

(57) **Abstract:** This invention comprises a method of treating migraine in a human comprising co-timely administering of a therapeutically effective amount of a 5-HT agonist coordinated with a therapeutically effective amount of an NSAID, particularly a long-acting NSAID, and particularly of the class of NSAIDs termed cyclooxygenase-2 inhibitors (COX-2 inhibitors) such as celecoxib (Celebrex[®]), rofecoxib (Vioxx[®]), meloxicam, piroxicam, JTE-522, L-745,337, and NS398, and in some instances, doses below those ordinarily considered as minimum effective doses as to one or both 5-HT agonist and long-acting NSAID. Dosage forms are included herein.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/03897

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 20870 A (POZEN INC) 22 May 1998 (1998-05-22) page 12, line 10-18; claims 5-7,20-28 page 19, line 8 -page 23, line 19 page 23, line 20 -page 24, line 5 ----	1,2, 21-23, 29-33
X	PAVEL AND BALUCH: "Formulation of Antimigraine Mixtures" STN HCA,XX,XX, vol. 8, no. 121, 22 August 1994 (1994-08-22), XP002078672 the whole document ----	1,5,21, 22,29, 31,32
A	HAAG: "Kombianalgetika in der Kopfschmerztherapie" DEUTSCHE APOTHEKER ZEITUNG,DE,DEUTSCHER APOTHEKER ZEITUNG, STUTTGART, vol. 4, no. 138, 22 January 1998 (1998-01-22), pages 43-48, XP002079370 ISSN: 0011-9857 table 1 ----	2,33,35
X	GB 2 135 884 A (SANDOZ LTD) 12 September 1984 (1984-09-12)	1,5,21, 22,29, 31,32
A	claims 1,15-18 ----	2,33,35
A	DE 195 42 281 A (BOEHRINGER INGELHEIM KG) 15 May 1997 (1997-05-15) claims 5,6,8 ----	1,2
A	WO 97 38986 A (SEARLE & CO) 23 October 1997 (1997-10-23) page 5, line 7-9 page 4, line 22-26 -----	1,2

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-23 and 25-38 relate to methods and compositions involving compounds defined by reference to desirable characteristics or properties, namely agonism of the 5-HT receptor, analgesic activity, anti-inflammatory activity, inhibition of COX-2, and establishing certain peak blood- or blood plasma levels of an (unspecified) compound. The claims cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT - for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). A compound cannot be sufficiently defined by its mechanism of action and/or its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Furthermore, the claims relate to an extremely large number of possible compositions and methods by means of the above expressions, as well as terms like "sub-MED amounts", "long-acting", "co-timely", and "about". The term "non-Non Steroidal Anti Inflammatory Drug" is confusing, as it should be taken to mean "Steroidal AID", which would render claims 31 and 32, and page 2, lines 30-31 of the description, contradictory. This term was read as "non-steroidal, non-opiate anti-inflammatory drug possibly not listed as anti-inflammatory".

The term "sub-MED amounts" (claims 26-28) is not sufficiently defined on page 7, lines 26-31, especially in view of the definition of "therapeutically effective amount" (page 9, under "B") which is used in independent claim 1, upon which claims 26-28 depend. Besides, page 7 does not define "sub-MED" amounts for all possible 5-HT agonists and (non-) NSAID analgesics.

The term "long-acting" (claim 35), although defined for some NSAIDs on page 8, under "A", does not specify the meaning of this term in relation to COX-2 inhibitors in general and in relation to celecoxib in particular.

The term "co-timely" (claims 29,33) is not sufficiently defined on page 15, under "C", lines 9-10.

Due to the above, a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the complete scope of the claims impossible.

Finally, the scope of claim 20 is not readily identifiable because of the wording: "less than about from about..." .

Consequently, the search has been carried out for those parts of the claims which appear to be clear, concise, supported and disclosed, namely those parts relating to the specific compounds, compositions and methods referred to in present claims 3-20, 22-24, 30-32, 34 and 36-40, and disclosed in the examples, with due regard to the description and to the general idea underlying the application.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims 24, 39 and 40 have been completely searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/US 00/03897

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0025779	A	11-05-2000	NONE		
WO 9806392	A	19-02-1998	AU 711741 B AU 3984597 A EP 0957914 A JP 20005065641 T US 5872145 A		21-10-1999 06-03-1998 24-11-1999 30-05-2000 16-02-1999
WO 9815275	A	16-04-1998	US 5891885 A AU 4806197 A EP 0932416 A US 6043244 A US 5939425 A		06-04-1999 05-05-1998 04-08-1999 28-03-2000 17-08-1999
WO 9820870	A	22-05-1998	US 6077539 A AU 5201098 A EP 1014961 A JP 2000507614 T		20-06-2000 03-06-1998 05-07-2000 20-06-2000
GB 2135884	A	12-09-1984	AU 2535584 A BE 899058 A CA 1228817 A CH 660303 A DD 216383 A DE 3407579 A DK 148884 A ES 530359 D ES 8608867 A FR 2542195 A GR 82005 A HU 34885 A IL 71176 A JP 59170014 A LU 85242 A NL 8400641 A NZ 207411 A PH 20258 A PT 78208 A,B SE 8401263 A US 4515802 A ZA 8401783 A		13-09-1984 03-09-1984 03-11-1987 15-04-1987 12-12-1984 13-09-1984 10-09-1984 01-09-1986 16-12-1986 14-09-1984 12-12-1984 28-05-1985 29-02-1988 26-09-1984 14-11-1984 01-10-1984 31-07-1987 14-11-1986 01-04-1984 10-09-1984 07-05-1985 30-10-1985
DE 19542281	A	15-05-1997	AU 706112 B AU 7623096 A BG 62511 B BG 102408 A BR 9611502 A CA 2232008 A CN 1202111 A CZ 9801498 A WO 9717971 A EP 0861081 A HU 9903489 A JP 2000500446 T NO 982172 A PL 326653 A SK 61398 A US 5942503 A		10-06-1999 05-06-1997 31-01-2000 30-12-1998 02-03-1999 22-05-1997 16-12-1998 14-10-1998 22-05-1997 02-09-1998 28-03-2000 18-01-2000 13-05-1998 12-10-1998 09-09-1998 24-08-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/03897

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9738986	A 23-10-1997	AU	2722797 A	07-11-1997
		BG	102916 A	31-08-1999
		BR	9708574 A	03-08-1999
		CA	2249009 A	23-10-1997
		CN	1216043 A	05-05-1999
		CZ	9802710 A	13-01-1999
		EP	0892791 A	27-01-1999
		HU	9901807 A	28-09-1999
		LT	98142 A, B	26-07-1999
		LV	12239 A	20-03-1999
		LV	12239 B	20-08-1999
		NO	984727 A	14-12-1998
		NZ	331542 A	29-07-1999
		PL	329276 A	15-03-1999
		SI	9720035 A	30-06-1999
		SK	124298 A	13-04-1999
		US	5932598 A	03-08-1999

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/03897

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61P25/06 A61K45/06 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 25779 A (MERCK & CO INC) 11 May 2000 (2000-05-11) page 4, line 9-19; claims 1-9 —	1-40
X	WO 98 06392 A (POZEN INC) 19 February 1998 (1998-02-19)	1,4-10, 21-23, 25-32
A	page 1-24; claims 1-15,18-20,23-34,37-52; examples —	33,35-38
X	WO 98 15275 A (ALGOS PHARM CORP) 16 April 1998 (1998-04-16)	1-3,5, 21,22, 29-33,36
A	page 14, line 28, paragraph 1.55 -page 15, line 22; claims 3,7,14,18 —	4,6,7, 35-37
	—/-—	

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

** document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

3 document member of the same patent family

Date of the actual completion of the international search

11 August 2000

Date of mailing of the international search report

21/08/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5018 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2640, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kanbier, D